New Claim 16. The method according to claim 15, wherein the muricin A, muricin B, muricin C, and muricin F are eluted from the seventh fraction of the Si gel column and further purified by a reversed-phase high performance liquid chromatography.

New Claim 17. The method according to claim 15, wherein the muricin D (4), muricin E (5), and muricin G (7) are eluted from the eighth fraction of the Si gel column and further purified by a reversed-phase high performance liquid chromatography.

New Claim 18. The anti-tumor composition according to claim 5, wherein said composition further comprises a pharmaceutically acceptable salt and/or ester in combination with a pharmaceutically acceptable carrier, auxiliary or excipient.

REMARKS

Applicant requests favorable reconsideration of the subject application in view of the amendments and the following remarks.

In the Office Action dated September 24, 2002, the term "Novel" in the title is objected to. Claims 1-9 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claims 1-9 are rejected under 35 U.S.C. §102(b) as being anticipated by McLaughlin et al (U.S. Patent No. 5,955,497).

Applicant acknowledges safe receipt of the Notice of References Cited (PTO-892).

In response, Applicant has amended the title, cancelled claims 3-4, amended claims 1-2, 5-6 and 9 and added new claims 10-18. No new matter has been introduced.

Applicant respectfully submits that the amendments have overcome the objection and rejections for the following reasons:

Objection of the Term in the Title

The term "Novel" in the title is objected to.

In response to the objection, Applicant has amended the title to remove the term "Novel" in favor of expediting the prosecution of this application. In no way that Applicant's amendment of the title should be construed to mean that Applicant agrees that the Annonaceous acetogenins from *Annona muricata* disclosed in this application are not novel, particularly since these acetogenins have not previously disclosed.

Claim Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-9 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, the Examiner indicates that the term "selectively" in claims 1-9 is a relative term that renders the claim indefinite. Additionally, the Examiner rejected Applicant's use of the term "substantially pure" as indefinite.

In response to these rejections, Applicant has amended the claims to remove the terms "selectively" and "substantially" from the claims.

However, Applicant disagrees with the Examiner's assertion that "the claimed acetogenin derivatives are known in the art per se and indeed naturally occur as tacitly conceded by applicants. A substantially pure form would be inherent." Applicant would like to point out that the claimed acetogenin derivatives in the present application are new and have not been disclosed before. In fact, all of the claimed acetogenin derivatives as described in claim 1 are isolated from seeds of A*nnona muricata* with purity greater than 95% and even as high as 99%

(page 3, lines 5-6 as originally filed). At such a high purity, the claimed acetogenin derivatives are technically almost pure.

Claim Rejections under 35 U.S.C. § 102(b)

Claims 1-9 are rejected under 35 U.S.C. 102(b) as being anticipated by McLaughlin et al (U.S. Patent No. 5,955,497, hereinafter, "McLaughlin").

Applicant respectfully traverses the rejections.

The claimed acetogenin derivatives of the present application are structurally distinctly different from the substantially pure acetogenin disclosed by McLaughlin.

McLaughlin discloses acetogenins isolated from *Annona squamosa*, which is different from Applicant's source of acetogenins (from *Annona muricata*). Also, as shown in the molecular structures at column 1, line 15 – column 2, line 60 and in claim 1 (column 8, line 54 – column 9, line 9), McLaughlin's acetogenins contain **two** THF rings in the carbon chain (hereinafter "two-ring acetogenins"). In contrast, only **one** THF ring exists in the carbon chain of the acetogenins (hereinafter "one-ring acetogenins") of the present invention. Furthermore, acetogenins contain multiple stereocentres (McLaughlin, column 1, lines 51-53). At such structural complexity, there is no simple, direct method to convert two-ring acetogenins (such as in McLaughlin) to one-ring acetogenins (such as in the present application). Nor can one reasonably deduce that the resultant one-ring acetogenins (even they it can be produced) will possess the same biological activity as the original two-ring acetogenins.

In short, McLaughlin fails to teach the acetogenins with only one THF rings and their uses as described in the present application.

In view of the foregoing, the objection and rejections have been overcome and the claims are in condition for allowance, early notice of which is requested. Should the application not be passed for issuance, the examiner is requested to contact the applicant's attorney to resolve the problem.

Attached hereto is a marked-up version of the changes made to the specification and claim by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Respectfully submitted,

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Date: December 24, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE TITLE:

The title has been amended as follows:

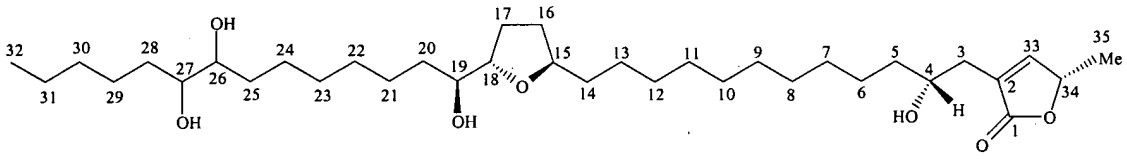
-- ~~NOVEL~~ CYTOTOXIC ANNONACEOUS ACETOGENINS FROM *ANNONA MURICATA* --

IN THE CLAIMS:

Claim 1 has been amended as follows:

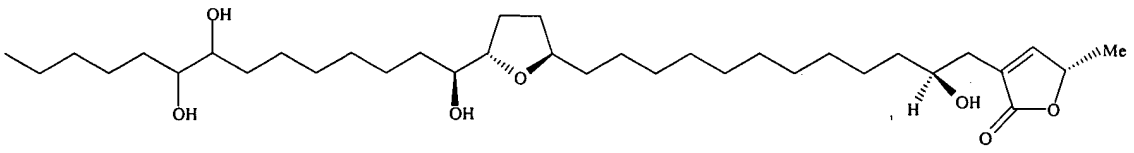
1. (Amended) Isolated and purified Annonaceous acetogenins ~~substantially pure~~ compounds having the structures of a-g~~.~~, wherein

a. muricin A has ~~having~~ the formula of ~~as~~:



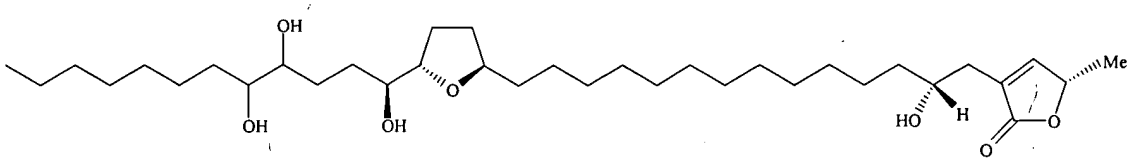
~~wherein the~~ said muricin A having an α, β-unsaturated γ-lactone with a hydroxyl group at C-4 ~~position~~, a mono-THF ring placed between C-15 and C-18 with one flanking hydroxyl in a threo conformation, two methylene groups of the mono-THF ring corresponding to a trans conformation, two hydroxyl groups at C-26 and C-27 as vicinal diol assigned as threo based, and the stereochemistry at C-34 on the γ-lactone fragment performed in (S)-configuration~~.~~;

b. muricin B has ~~having~~ the formula of ~~as~~:



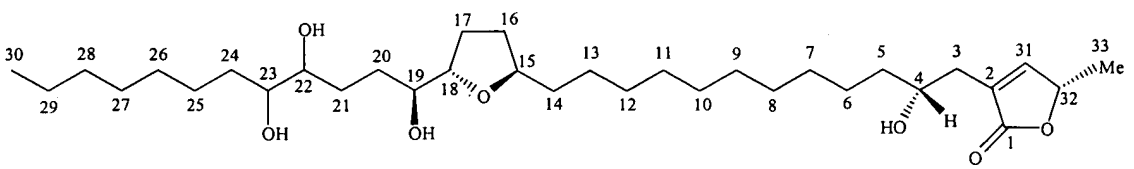
~~wherein the~~ said muricin B having an α, β-unsaturated γ-lactone with a hydroxyl group at C-4 ~~position~~, a mono-THF ring placed between C-15 and C-18 with one flanking hydroxyl in a trans/threo conformation, two methylene groups of the mono-THF ring corresponding to a trans conformation, two hydroxyl groups at C-26 and C-27 as vicinal diol assigned as threo based, and the stereochemistry at C-34 on the γ-lactone fragment performed in (S)-configuration~~.~~;

c. muricin C has ~~having~~ the formula of:



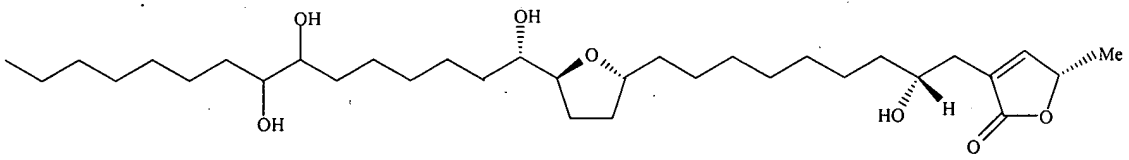
~~wherein the~~ said muricin C having an α, ß-unsaturated γ-lactone with a hydroxyl group at C-4 ~~position~~, a mono-THF ring placed between C-17 and C-20 with one flanking hydroxyl in a trans/threo or threo/trans conformation, two hydroxyl groups at C-24 and C-25 as vicinal diol assigned as threo based, and the stereochemistry at C-34 on the γ-lactone fragment performed in (S)-configuration~~.~~;

d. muricin D has ~~having~~ the formula of:



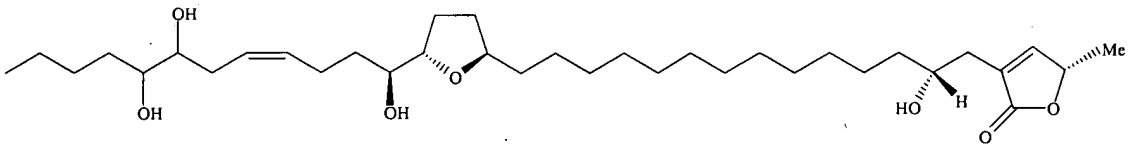
~~wherein the~~ said muricin D having an α, β-unsaturated γ-lactone with a hydroxyl group at C-4 ~~position~~, a mono-THF ring placed between C-15 and C-18 with one flanking hydroxyl in a threo/trans conformation, two hydroxyl groups at C-22 and C-23 as vicinal diol assigned as threo based~~.~~;

e. muricin E has ~~having~~ the formula of:



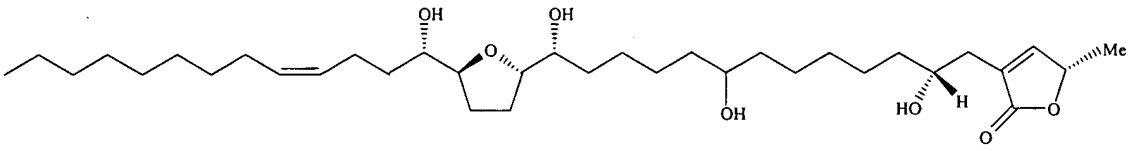
~~wherein the~~ said muricin E having an α, β-unsaturated γ-lactone with a hydroxyl group at C-4 ~~position~~, a mono-THF ring placed between C-12 and C-15 with one flanking hydroxyl in a threo/trans conformation, two hydroxyl groups at C-22 and C-23 as vicinal diol assigned as threo based~~.~~;

f. muricin F has ~~having~~ the formula of:



~~wherein the~~ said muricin F having an α, β-unsaturated γ-lactone with a hydroxyl group at C-4 ~~position~~, a mono-THF ring placed between C-17 and C-20 with one flanking hydroxyl in a threo/trans conformation, two hydroxyl groups at C-27 and C-28 as vicinal diol assigned as threo based, and a double bond determined at C-24/C-25~~.~~; and

g. muricin G has ~~having~~ the formula of:



~~wherein the~~ said muricin G having an α, β-unsaturated γ -lactone with a hydroxyl group at C-4, a mono-THF ring placed between C-16 and C-19 with one flanking hydroxyl in a threo/trans/threo conformation, one hydroxyl groups formed at C-10, a double bond determined at C-23/C-24, and the stereochemistry at C-34 on the γ-lactone fragment performed in (S)-configuration.

Claim 2 has been amended as follows:

2. (Amended) A method for ~~substantially purified~~ isolating and purifying the Annonaceous acetogenin compound according to ~~extract of~~ claim 1 ~~from the species *Annona muricata*, wherein the method~~ comprising:

extracting muricins from *Annona muricata* seeds ~~repeatedly~~ with MeOH to obtain an methanol extract at room temperature;

evaporating and partitioning the ~~combined MeOH~~ MeOH extracts in a ~~to yield~~ $CHC1_3$ and aqueous mixture ~~extracts~~, whereby said Annonaceous acetogenins compounds are partitioned in the $CHC1_3$ layer of the $CHC1_3$ and aqueous mixture; and

further separating the Annonaceous acetogenins compounds of said ~~the~~ $CHC1_3$ layer ~~into ten fractions~~ by column chromatography ~~on a Si gel with a gradient system of *n*-hexane-CHC13 and CHC13-MeOH~~;

~~combining the eighth and ninth fractions together and then further separating into ten sub-fractions by column chromatography; and~~

~~isolating and purifying the Annonaceous acetogenins compounds from the ten sub-fractions~~.

Claims 3-4 have been cancelled.

Claim 5 has been amended as follows:

5. (Amended) An anti-tumor composition ~~selectively~~ comprising an effective amount of ~~substantially~~ at least one Annonaceous acetogenins compounds ~~pure muricins of~~ according to claim 1 ~~wherein the muricins are effective and acted as an anti-tumor agent and selectively combined with a pharmaceutically acceptable salt, ester and carrier in the anti-tumor composition~~.

Claim 6 has been amended as follows:

6. (Amended) The Annonaceous ~~annonaceous~~ acetogenins compounds as claimed in claim 1, wherein the Annonaceous acetogenins compounds ~~substantially pure muricins~~ are ~~selectively~~ used for ~~the preparation of a pharmaceutical composition for the~~ treatment of ~~a~~ patients having a tumor.

Claim 9 has been amended as follows:

9. (Amended) A method for treating hepatoma cancer~~, said method~~ comprising administering to a patient afflicted with hepatoma cancer an effective amount of a pharmaceutical composition comprising ~~a substantially~~ at least one Annonaceous acetogenins compounds according to ~~pure bioactive compound selected from the group consisting of~~

~~muricins of claim 1~~ and a pharmaceutically acceptable salt~~,~~ and ester~~,~~ in combination with pharmaceutically acceptable carrier, auxiliary or excipient ~~or carrier~~.